REMARKS

I. STATUS OF CLAIMS

Claims 17, 20-22, and 24-30 are pending in the present application. Claims 26-27, and 30 are allowed. Claim 17 has been amended. Claims 18 and 19 are being cancelled. Claims 17-19, 21-22, and 24-25, are rejected. Claim 29 is withdrawn.

Claim 17 has been amended to recite "the first antigen is a capsular oligosaccharide from serogroup C *N. meningitidis* (NmC) conjugated to CRM_{197}." Support for this amendment may be found at least at page 2, lines 7-9 of the specification, and originally filed claim 4.

No new subject matter has been added, thus entry of the amendments is respectfully requested. Cancellation of claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the subject matter of the cancelled claims.

II. WITHDRAWN OBJECTIONS AND REJECTIONS

Applicants acknowledge and thank the Office for withdrawing the objection to the specification.

Applicants also acknowledge and thank the Office for withdrawing the new matter rejection of claims 24 and 28.

Applicants note that the Office did not state whether the rejection of claim 28 under 35 U.S.C. § 112, second paragraph, has been withdrawn. Given that the amendment to claim 28 was acknowledged by the Examiner, that the new matter rejection of claim 28 was withdrawn, and that the Office has not maintained the rejection in the pending Advisory Action, Applicants presume that the indefiniteness rejection has also been withdrawn.

III. REJECTION UNDER 35 U.S.C. § 103(A) MAINTAINED

Claims 17-19, 22 and 25

Claims 17-19, 22 and 25 are rejected under § 103(a) as allegedly being unpatentable over Granoff *et al*. (*infect. Immun.* 65: 1710-1715, May 1997, of record) (Granoff *et al.*, 1997) in view of Granoff *et al*. (*J. Pediatr.* 121: 187-194, 1992) (Granoff *et al.*, 1992), Vella *et al*. (*Biotechnology* 20: 1-22, 1992) and Frasch (*In*: *Development and Clinical Uses of Haemophilus B conjugate Vaccines*. (Ed) Willis *et al.* M. Dekker, New York, pages 435-453, 1994).

To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection and its supporting remarks.

As a preliminary matter, Applicants respectfully point out that independent claim 17 has been amended to require that the claimed capsular oligosaccharide from serogroup C *N. meningitidis* (NmC) be conjugated to CRM_{197}. Moreover, claims 18 and 19 have been cancelled, making their rejection moot.

Applicants respectfully maintain that the Office has failed to establish a *prima facie* case of obviousness, as one of skill in the art would not have had a reasonable expectation of success in combining the teachings of the cited references to produce the claimed invention.

The Office states that one of ordinary skill in the art at the time the invention was made would have been motivated to replace the Hib-CRM_{197} conjugate of Granoff's (1997) immunogenic combination vaccine composition with Granoff's (1992) more immunogenic Hib PRP-Nmb OMV conjugate to produce the immunogenic composition of the instant invention, for the expected benefit of providing a combination conjugate vaccine that includes a Hib conjugate that is more immunogenic, elicits earlier acquisition of serum antibody, and that has a number of unique properties.

However, the Office has not demonstrated that the cited references teach or suggest how the Hib PRP-NmB OMV conjugate interacts with Granoff's (1997) NmC-CRM_{197} conjugate.

Applicants respectfully assert that one of skill in the art would not have a reasonable expectation of success in combining Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate to produce the currently claimed invention, as that combination would have yielded unpredictable results. MPEP § 2143.02 makes clear that to show a reasonable expectation of success, it must be shown that combining the teachings of the references "would have yielded nothing more than predictable results to one of ordinary skill in the art," (emphasis added)..

Applicants respectfully point out that the NmB OMV carrier taught in Granoff *et al.*, 1992 is not the same as the CRM_{197} carrier taught in Granoff *et al.*, 1997. Thus teachings regarding interactions between Hib PRP-CRM_{197} and NmC-CRM_{197} conjugates would not be informative with regard to interactions between Hib PRP-NmB OMV and NmC-CRM_{197} conjugates. Moreover, combining vaccine components particularly where the carriers are from different classes can produce unpredictable results. For example, it would have been unpredictable whether combining Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate would lead to an adverse interaction between the very different carriers. Given this unpredictability, one of skill in the art would not have been motivated to combine the Hib PRP-NmB OMV conjugate with the NmC-CRM_{197} conjugate. Rather, one of skill in the art would have been motivated to minimize the possibility of an adverse interaction between the Hib PRP-NmB OMV conjugate and the NmC-CRM_{197} conjugate. One such method of minimizing the possibility of an adverse interaction would be to replace the CRM_{197} carrier of NmC with the NmB-OMV carrier. One of skill would have been motivated to replace the CRM_{197} carrier protein of the NmC conjugate with the NmB-OMV carrier not only to avoid any possible adverse interactions between Hib PRP-NmB OMV and NmC-CRM_{197}, but *also*, assuming that the Examiner is correct regarding the OMVs general effect upon antigenicity of capsular polysaccharides, for the expected benefits of increased immunogenicity, earlier acquisition of serum antibody, and the number of unique properties of the NmB-OMV carrier. However, the currently amended claims require that NmC be conjugated to CRM_{197}, and thus would not read upon such a modified vaccine composition where both NmC and Hib are conjugated to NmB OMVs. Therefore, one of skill in the art would have had no reason to

combine Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate to produce the currently claimed invention.

Even if one of skill in the art were to combine Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate, there would still not be a reasonable expectation of success in that combination as it would be unpredictable whether the combination would result in the expected benefits of the Hib PRP-NmB OMV conjugate alone. Granoff et al., 1992 teach that the Hib PRP-NmB OMV conjugate alone results in a higher immune response after a single injection compared to the Hib-CRM_{197} conjugate. However, Fig. 1 of Granoff et al., 1992 also indicates that three injections were required for a CRM_{197} conjugate to give a strong immune response. Given this difference in immune response, if one of skill in the art were to combine NmC-CRM_{197} with the Hib PRP-NmB OMV conjugate, as suggested by the Office, it would be unpredictable whether the combination would result in the expected benefit of a strong immune response after a single injection. Or put another way, why would one of skill in the art combine a vaccine that requires one dose with a vaccine that requires three doses? This observation further supports the Applicants' assertion that one of skill in the art would replace the NmC-CRM_{197} with an NmC-NmB OMV so that the single dose would provide a similar response to NmC as to the Hib PRP.

Furthermore, Applicants also respectfully maintain that there would be no reasonable expectation of success in combining Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate to produce the currently claimed invention, given the unpredictability of using MF59 with NmB OMVs. Applicants respectfully point out that the Office has not demonstrated that the cited references provide any indication of how MF59 interacts with NmB OMVs. MPEP § 2143(B) makes clear that "combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art." As noted above, NmB OMVs are distinct from CRM_{197}, consequently teachings regarding interactions between MF59 and conjugates containing CRM_{197} would not be informative regarding interactions between MF59 and conjugates containing NmB OMVs. Despite the Office's assertion that Granoff *et al.*, 1997 "had already established at the time

of the invention that MF59 could successfully be combined with a multivalent combination vaccine comprising more than one carbohydrate-containing elements and protein elements," (Advisory Action, top of page 8), the Office has not demonstrated that Granoff *et al.*, 1997 give any indication that MF59 could be predictably combined with NmB OMVs. Without such knowledge it would have been unpredictable whether combining the Hib-NmB OMV conjugate with the MF59 adjuvant would result in Granoff's (1997) expected benefits of using MF59. Thus, there would have been no reasonable expectation of success in combing Graff's (1992) Hib-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate and the MF59 adjuvant to yield the currently claimed invention.

The Office also states that "Applicants appear to argue that the combination of references fail because the prior art does not have anticipatory references regarding all elements of the invention," (Advisory Action, top of page 9). However, Applicants respectfully point out that Applicants are not arguing that the combination of references fail because the prior art does not have anticipatory references. Rather Applicants are respectfully asserting that there would be no reasonable expectation of success in combining the teachings of the cited references to produce the claimed invention, as that combination would not have yielded predictable results (MPEP § 2143.02).

With regard to claims 18 and 19, Applicants maintain their traversal of the rejection and its supporting remarks on the ground that there would be no reasonable expectation of success in combining the teachings of the cited references. However, as noted above, and in order to advance prosecution but without prejudice or disclaimer, Applicants have amended independent claim 17 to recite that NmC is conjugated to CRM_{197} and have cancelled claims 18 and 19, making the rejection moot.

For at least the reasons set forth above, Applicants respectfully maintain that claims 17, 22 and 25 would not be obvious in view of Granoff *et al.*, 1997, Granoff *et al.*, 1992, Vella *et al.*, and Frasch. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 21

The rejection of claim 21 under § 103(a) as allegedly being unpatentable over Granoff *et al.*, 1997 as modified by Granoff *et al.*, 1992, Vella *et al.*, Frasch, and further in view of Dalseg *et al.* (In: Vaccines 96. (Ed) Brown F. Cold Spring harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996, of record) is maintained.

Applicants respectfully maintain their traversal of the rejection and its supporting remarks. As discussed above, the Office has failed to establish a *prima facie* case of obviousness, as one of skill in the art would not have a reasonable expectation of success in combining the teachings of the cited references to yield the currently claimed invention. Applicants respectfully assert that combining Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate and MF59 would have yielded unpredictable results (MPEP § 2143.02). The Office has not demonstrated how Dalseg *et al.* impacts the predictability of combining the teachings of Granoff *et al.* 1997 and Granoff *et al.* 1992 to yield the currently claimed invention. Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 24

Claim 24 is rejected under § 103(a) as allegedly being unpatentable over Granoff *et al.*, 1997 as modified by Granoff *et al.*, 1992, Vella *et al.*, Frasch, and further in view of Seid (US 6,638,513, of record) ('513) or Granoff (WO 98/58670) ('670).

Applicants respectfully maintain their traversal of the rejection and its supporting remarks. As discussed above, the Office has failed to establish a *prima facie* case of obviousness, as one of skill in the art would not have a reasonable expectation of success in combining the teachings of the cited references to yield the currently claimed invention. Applicants respectfully assert that combining Granoff's (1992) Hib PRP-NmB OMV conjugate with Granoff's (1997) NmC-CRM_{197} conjugate and MF59 would have yielded unpredictable results (MPEP § 2143.02). The Office has not demonstrated how Seid ('513) or Granoff ('670) impacts the predictability of combining the

teachings of Granoff *et al.* 1997 and Granoff *et al.* 1992 to yield the currently claimed invention. Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

IV. OBJECTION TO THE CLAIMS AND ALLOWABLE CLAIMS

The Office has objected to claim 20 as being dependent upon a rejected base claim, but found that the claim would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. For the reasons stated above, Applicants respectfully assert that the objected claim depends from an allowable claim. Applicants therefore respectfully request that this basis for objection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002100100**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By /Otis Littlefield/
Otis B. Littlefield
Registration No.: 48,751

MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: 415.268.6846
Fax: 415.268.7522